The effectiveness of *Jamblang* (*Syzygium cumini (L) Skeels*) extract on the atherogenic index in a diabetic rat model
Efektivitas ekstrak buah Jamblang (Syzygium cumini (L) Skeels) terhadap indeks aterogenik pada tikus model diabetes

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Abstract

Jamblang fruits (*Syzygium cumini (L.) Skeels*) have the potential as an antioxidant by facilitating glucose and lipid metabolism for reducing the atherogenic index (AI). This study aimed to explore the effect of the *Jamblang* extract on the atherogenic index in a diabetic rat model. This pre- and post-control group design study was conducted in the Pharmacology Laboratory of Universitas Sumatera Utara. Twenty-five rats were divided into five groups. Alloxan 120 mg/kg BW was administrated intraperitoneally, and the rats' fasting blood glucose levels were measured four days later. Group I (negative control) were treated with aqua dest, group II (positive control) was treated with glibenclamide 1,25 mg /kg BW, and group III, IV, and V were given an extract of *Jamblang* at a dose of 125, 250, and 500 mg/kg BW for seven days. Trigliserida and HDL-C measured using spektrofotometer microlab. The data were subjected to the Kruskal-Wallis test to examine the effect of *Jamblang* extract in different doses on the atherogenic index, followed by a Mann-Whitney Post hoc test. The result revealed that the extract *Jamblang* dose of 125, 250, and 500 mg/kg BW significantly decreased the atherogenic index (p value= 0,012<0,05). In conclusion, the *Jamblang* (*Syzygium cumini (L.) Skeels*) with the best-tested dose was 500 mg/kgBW to decrease the atherogenic index until 0,42 in vivo study.

Keywords: *Syzygium cumini* extract, atherogenic index, alloxan, triglyceride

Abstrak

Buah *Jamblang* memiliki potensi sebagai antioksidan dengan memfasilitasi metabolisme glukosa dan lipid sehingga dapat menurunkan indeks aterogenik (AI). Penelitian ini bertujuan untuk menentukan efek ekstrak *Jamblang* (*Syzygium cumini (L.) Skeels*) terhadap indeks aterogenik pada tikus model diabetes. Penelitian ini adalah *pre and post control group design* dan dilakukan di Laboratorium Farmakologi Universitas Sumatera Utara. Dua puluh lima ekor tikus dibagi dalam 5 kelompok. Aloksan 120 mg/kg BB diberikan secara intraperitoneal, tikus diukur kadar glukosa darah puasanya 4 hari berikutnya. Kelompok I (kontrol negatif) diberi aquadest, kelompok II (kontrol positif) diberi Glibenklamid 1,25 mg/kg BB, kelompok III, IV dan V diberi ekstrak buah *Jamblang* dengan dosis 125, 250, and 500 mg/kg selama 7 hari. Kadar trigliserida dan HDL-C diukur menggunakan spektrofotometer microlab. Data dianalisis menggunkan uji *Kruskal-Wallis* untuk menilai pengaruh perbedaan dosis ekstrak Syzygium cumini (L.) Skeels terhadap indeks aterogenik dilanjutkan dengan uji Post hoc *Mann-Whitney.* Hasil penelitian menunjukkan bahwa ekstrak buah *Jamblang* dosis 125, 250, and 500 mg/kg menurunkan indeks aterogenik secara signifikan (p value=0,012<0,05). Kesimpulan penelitian bahwa ekstrak buah *Jamblang* dosis terbaik 500 mg/kg BW mampu menurunkan indeks aterogenik hingga 0,42 pada uji invivo.

Kata Kunci: Ekstrak *Jamblang*, indeks aterogenik, aloksan, trigliserida

Introduction

Diabetes mellitus (DM) is one of the degenerative diseases that is still a concern around the world. Epidemiological data from the International Diabetes Federation (IDF) reports that around 536,5 million of the world's population aged 20–79 years will suffer from diabetes in 2021. IDF also reported that Indonesia has the 5th highest number of diabetes cases in the world. It is reported that there are around 19,5 million diabetics in Indonesia, and it is estimated that there will be an increase of 28,6 million diabetics in 2024 (IDF Diabetes Atlas, 2021). The prevalence of DM in Aceh was recorded at 1,8% until 2013 and continued to increase, with prevalence reaching 2,5% in 2018 (Riskesdas, 2018).

Diabetes mellitus develops as a result of the accumulation of complicated metabolic abnormalities caused by decreased insulin secretion and/or function. The disease affects the endocrine system, resulting in glucose intolerance and hyperglycemia (Hartoyo et al., 2011). This condition will stimulate the formation of atherogenic plaques through smooth muscle proliferation, LDL (low-density lipoprotein) deposition in plaque, and connective tissue formation (Daniels et al., 2011). Therefore, DM sufferers are at risk of 2–4 times more atherosclerosis compared to non-DM sufferers (Yulsam et al., 2015).

The Ministry of Health of the Republic of Indonesia has developed a strategic plan that outlines a national health objective focused on establishing a resilient health security system. This is pursued through strengthening the production of medical devices, medicinal raw materials, medicines, traditional medicines, and vaccines in the country. This effort is expected to improve the prevention and control of non-communicable diseases (Kemenkes, 2022).

Diabetes Mellitus (DM) is a risk factor for cardiovascular and cerebrovascular disorders. Diabetes-related hyperglycemia can produce endothelial dysfunction as an early alteration in the emergence of atherosclerotic problems (Sudoyono et al., 2009). Prospective research indicates that the increase in the prevalence of the disease in people with DM is caused by a narrowing of the artery lumen and that unstable or progressive atherosclerosis processes account for 80% of patients' deaths (Farkouh et al., 2011).

Diabetes patients would need a lot of money to undertake treatment and maintain physical health, especially if they have clinical issues (Setiawati, 2012). The prognosis of diseases that are difficult to treat permanently aggravates this condition, causing sufferers to become bored and stop taking their medications (Pratita, 2013). Therefore, patients tend to seek alternative treatments that are easily accessible and have few adverse effects, such as the use of herbs as traditional medicine (Setiawati, 2012).

Some plants have been shown to lower blood glucose levels (BG). Red dragon fruit has been shown to lower BG in type 2 diabetes patients (Ayuni, 2020). Bitter melon has also been shown to reduce BG in alloxane-induced rats (Puspitasari & Choerunisa, 2021). However, its use is sometimes based solely on experience or is empirically constrained. *Jamblang* (*Syzygium cumini (L.) Skeels*), as some Acehnese believe, is effective for lowering BG; however, few are aware of the veracity of these properties based on clinical and preclinical investigations (Suhirman & Winarti, 2001).

Jamblang extract contained oleanolic acid that can inhibit the involvement of free radicals in plaque or atheroma (Dalimartha & Adrian, 2011). Flavonoids (anthocyanins), resins, tannins, gallic acid, phytomelin glucosides, and alpha-phytosterol are all found in *Jamblang* (Ayyanar & Babu, 2012). *Jamblang* has high antioxidant activity due to its anthocyanin content. This activity is quite similar to that of butyl hydroxytoluene (BHT), a synthetic antioxidant that is routinely consumed (Marliani et al., 2014).

Jamblang has been demonstrated effective in reducing. Research on the efficacy of reducing the risk of complications caused by DM is not widely known. This study aimed to measure the effectiveness of *Jamblang* fruit (skin, flesh, and seeds) in reducing the risk of atherosclerosis (atherogenic index/IA) in white rats (*Rattus norvegicus L.*) male Wistar strain induced by alloxane.

Methods

This research is in a true experimental laboratory using a pre-posttest control group design. The sample was a white rat (*Rattus norvegicus L.*) male Wistar strain divided into 5 groups, with 5 rats per treatment group.

Determination of sample size using Federer's experimental sample size formula:

$$(n-1)(t-1) \geq 15$$

Information:
n = number of samples per treatment group
t = number of treatment groups

Based on the formula above, a sample size calculation with t = 5 is carried out, and then we get:

$(n-1)(5-1) \geq 15$
$(n-1)4 \geq 15$
$4n \geq 19$
$n \geq 4,7 \approx 5$

The calculation results showed that the total number of samples used was 25 mice. The treatment group will be given *Jamblang* fruit extract at doses of 125 mg/kgBW, 250 mg/kgBW, and 500 mg/kgBW, respectively. The manufacture of *Jamblang* fruit extract is carried out at the Chemical Engineering Laboratory of Malikussaleh University, North Aceh.

The Pharmacology Laboratory, Faculty of Pharmacy, University of North Sumatra, Medan, was used for experimental animal maintenance and treatment, as well as atherogenic index (Indeks Atherogenik/IA) measurements. The research has obtained ethical clearance from the Aceh Young Health Research Institute (Lembaga Peneliti Muda Kesehatan Aceh/LPMKA) in Indonesia with number 06/KOMET/LPMKA/2015.

Making extracts begins with *Jamblang* fruit being sorted wet to separate, then dried in an oven at a temperature of 37 °C to 40 °C. Further fruit cutting is done to speed up the grinding process, and then simplistic is mashed using a blender.

Jamblang fruit powder was macerated with 96% methanol for 24 hours at room temperature. The precipitate is further filtered and stored in the filtrate, while residual immersion is re-applied in the same solvent. The treatment is repeated 5 times. Furthermore, the resulting filtrate is then accommodated, and the solvent is evaporated using a rotary evaporator at a temperature of 50 °C until a viscous extract is obtained. The water content in the viscous

extract is removed using a freeze dryer to obtain a dry extract.
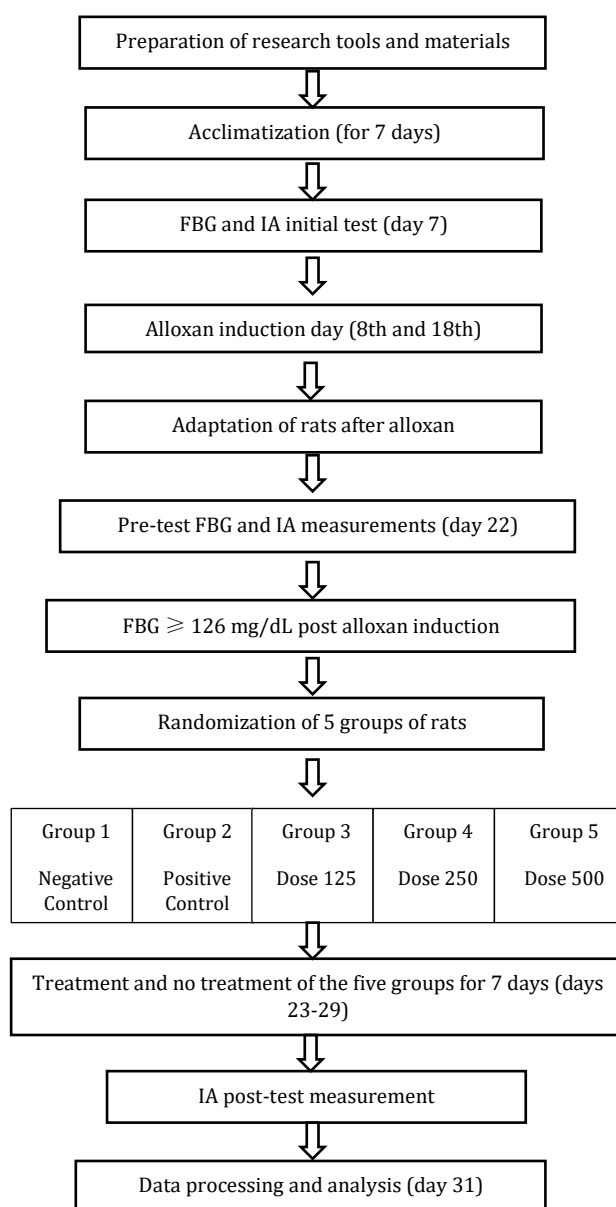
Figure 1. Research flow

Preparation of aloxane solution by means of alloxane powder dissolved with 0,9% NaCl up to a volume of 5 mL. Aloxane induction dose in intraperitoneal and subcutaneous rats using a dose of 120 mg/kgBW.

Making Glibenclamide solution by making a suspension by dissolving the total dose in 1 group into 5 mL of aqueous solution to be given orally using a syringe sonde. Glibenclamide is given at a dose of 1,25 mg/kgBW.

Rats were made into DM or FBG conditions $\geq$ 126 mg/dL by inhibiting the work of the rat's pancreas. Before the first step, FBG

and IA mice were examined first to exclude mice against the exclusion criteria (the initial test). Rats in each group were given alloxane as much as 120 and 110 mg/kg BW in a 0,9% NaCl solution intraperitoneally to produce DM conditions (Setyowati, 2014).

Blood glucose levels in rats were measured using a microlab 300 spectrophotometer using the GOD-PAP (Glucose Oxidase-Peroxidase Aminoantipyrine Phenol) method. The atherogenic index is also measured using a microlab 300 spectrophotometer; the TG and HDL-C values obtained are fed into the formula. Sufficient blood sampling from the lateral veins of the tail. Blood serum measured TG and HDL-C levels using a perectation kit with an enzymatic-calorimetry method by Cholesterol Oxidase-Peroxidase Aminoantipyrine Phenol (CHOD-PAP).

Group I (the negative control) was given aquadest; group II (the positive control) was given Glibenclamide at 1,25 mg/kg BW; and groups III, IV, and V were given *Jamblang* fruit extract at doses of 125 mg/kg BW, 250 mg/kg BW, and 500 mg/kg, respectively. The dose level is then formed into a solution with 0,5% CMC Na as the solvent, and the volume of administration is calculated (in the range of 0,65 mL to 1.40 mL), which will be administered orally for 7 days with a syringe. Seven days after treatment or without treatment, rat AI measurements were carried out (post-test). Before the examination, the rats were satisfied for 8 to 16 hours. An AI examination takes enough blood from the lateral veins of the tail.

The processing of this research data in the form of TG and HDL-C values obtained with a microlab 300 spectrophotometer is included in the atherogenic index formula, according to (Bittner et al., 2009).

$$IA = \log (\text{Trigliserida/HDL-C})$$

Atherogenic indices of rats before and after treatment (*Jamblang* fruit extract and glibenclamide) and without treatment were shown in the Mean±SD.

Before testing bivariate analysis, the data is examined based on the Shapiro-Wilk test (number of samples ≤ 50), which aims to see the distributed data. All data is not normally distributed. The data were analyzed using the Kruskal-Wallis test to assess the effect of differences in extract concentrations on the AI index. Then we continued with the Mann-Whitney test to determine the best concentration of *Jamblang* fruit extract against reducing AI with a significance level of 95%.

Result and Discussion

Average Description of FBG (Fasting blood Glucose) and AI After Aloxane Injection

Aloxane injection doses of 120 mg/kg BB administered intraperitoneally can increase FBG and AI in rats. The average FBG of rats increased from 80,24±15,08 mg/dL to 190,68±104,97 mg/dL, while the mean AI value increased from 0,08±0,05 to 0,89±0,23.

Analysis of the Average AI Pre-Post Test for Each Group

The average AI value of rats in each group decreased after treatment or without treatment, The paired samples t test revealed significant differences from pre-test and post-test AI in all groups (Table 1).

Table 1. Atherogenic index levels in control and the treatment groups

Group	Pre-test (Mean ± SD)	Post-test (Mean ± SD)	Δ (Mean ± SD)	p value
Group I	0,87 ± 0,15	0,65 ± 0,09	0,22 ± 0,06	0,005*
Group II	0,85 ± 0,13	0,61 ± 0,09	0,24 ± 0,04	0,003*
Group III	0,85 ± 0,30	0,44 ± 0,15	0,41 ± 0,15	0,006*
Group IV	0,78 ± 0,15	0,41 ± 0,08	0,37 ± 0,07	0,000*
Group V	1,12 ± 0,29	0,70 ± 0,30	0,42 ± -0,01	0,000*

*Significant differences between groups according to the Paired Samples T-test (p < 0,05)

Analysis of Difference AI Reduction Between Groups

The data used in this analysis was a difference in AI reduction (pre-test and post-test) between group. The Kruskal-Wallis test showed a value of p= 0,012 (p <0,05), revealed that *Jamblang* (*Syzygium cumini*) extracts gave a significant effect on AI reduction between groups.

Furthermore, a Mann-Whitney Post hoc test was conducted to identify the optimal concentration of *Jamblang* (*Syzygium cumini*) extract in AI reduction (Table 2).

Table 2. Mean differences of the atherogenic index in control and the treatment groups

Parameters	I	II	III	IV	V
Average Atherogenic Index	$0,22 \pm 0,06$	$0,24 \pm 0,04^b$	$0,41 \pm 0,15^a$	$0,37 \pm 0,07^{ab}$	$0,42 \pm -0,01^{ab}$

Mean (n=5), a: Significant differences with the control group, b: significant differences between treatment groups based on the Post Hoc Test (Mann-Whitney) ($p < 0,05$).

Post-hoc test (Mann-Whitney) analysis found that there was no significant difference in the difference in AI reduction between groups I and II, However, there was a significant difference in the comparison of the negative control group and the *Jamblang* fruit extract group at each dose (groups III, IV, and V) with a p value of $< 0,05$.

The comparison of AI between groups II, IV, and V showed significant differences with p values $< 0,05$, While comparisons between other groups did not show significant differences in the difference in AI decline, such as in groups II and III, the comparison of the *Jamblang* fruit extract group in group III with groups IV and V and the comparison of the *Jamblang* fruit extract group in group IV with group V.

Atherogenic Index of Diabetic Rats

Diabetes mellitus is consistently characterized by abnormal lipid profiles and elevated AI, leading to the assumption that DM is an important risk factor for cardiovascular diseases such as atherosclerosis (Winarsi et al,, 2013), This study showed that all experimental mice injected with alloxane were found to be in a state of DM, which was also accompanied by an increase in AI, Aloxane is a diabetogenic substance that is involved in the formation of reactive oxygen and disrupts intracellular calcium homeostasis, which significantly affects peripheral insulin synthesis and sensitivity (Szkudelski, 2001).

Insulin plays an important role in glucose and lipid metabolism; therefore, impaired insulin synthesis and function are influenced by BG and lipid profiles, The role of lipids in pathological changes works by increasing the incidence of atherosclerosis, so that in diabetic conditions there will be an increase in AI (Winarsi et al., 2013).

The atherogenic index is an indicator to determine the risk of atherosclerosis, The trigger for the formation of plaque can be determined by the high ratio obtained to the AI value, Several studies have shown index assessment in the form of the triglycerine/HDL-C ratio (TG/HDL-C) to be a good predictor of cardiovascular disease (Da Luz et al., 2008).

Effectiveness of *Jamblang* Fruit Extract

The difference in AI reduction between the positive control group and the *Jamblang* fruit extract group at a dose of 250 mg/kg body weight and a dose of 500 mg/kg BW was significantly different ($p < 0,05$), which means that giving *Jamblang* fruit extract at that dose can significantly reduce AI better than giving glibenclamide. However, AI reduction between the *Jamblang* fruit extract group dose of 125 mg/kg body weight compared to glibenclamide was not significantly different ($p > 0,05$). The atherogenic index reduction was not significantly different between the Jamblang extract group dose of 125 mg/kg BW, 250 mg/kg BW and 500 mg/kg BW. However, increasing the dose of the *Jamblang* fruit extract from 125 mg/kg BW to 250 mg/kg BW and 500 mg/kg BW showed better effectiveness ($p < 0,05$) in reducing AI compared to the glibenclamide dose of 1,25 mg/kg BW.

The *Jamblang* fruit extract was significantly effective in reducing AI in diabetic rats because contained secondary metabolites such as flavonoids. These essentials materials play a role as antioxidant that inhibit lipid absorption (Sharmila et al., 2007).

These findings showed that giving *Jamblang* fruit extract with a flavonoid content of 12,3 grams facilitated glucose and lipid metabolism. The *Jamblang* fruit and seeds contain significant amounts of antioxidant compounds such as phenolic acids, flavonoids, and anthocyanins. These bioactive compounds are helpful in preventing various metabolic syndromes. The *Jamblang* fruit extract in

hyperglycemic rats showed a decrease in BG by 12,29% and increased insulin levels by about 6,19% (Raza et al., 2017). Flavonoids can stimulate peripheral glucose use through increased glycolytic and glycogen pathways while inhibiting the mechanisms of glycogenolysis and gluconeogenesis. The flavonoid content in *Jamblang* fruit extract makes it possible to regulate blood glucose so that levels go down. The decrease in BG due to the role of flavonoids in *Jamblang* fruit extract causes plasma lipid levels to also decrease. The content of active substances in *Jamblang* fruit can prevent the occurrence of atherosclerosis (Dalimartha & Adrian, 2011). The results of other studies concluded that *Jamblang* fruit proved to act as an anticholesterol (Ferry et al., 2015).

In addition to flavonoid D, the *Jamblang* fruit extract also contains oleanolic acid, which is a triterpenoid antioxidant. It was reported that administration of triterpenoid-rich *Jamblang* fruit extract (60 mg/rat) once daily for ten days in streptozotocin-induced diabetic mice resulted in a decrease in serum free fatty acid (FFA) and triglyceride levels in diabetic rats (Xu et al., 2018). The mechanism of action involves suppressing the role of free radicals, which act as one of the causes of diabetes mellitus pathology. *Jamblang* fruit extract may play a role in suppressing the process of plaque formation or atheroma and is also able to repair damaged cells so that they can regenerate properly. Currently available oral antidiabetics do not recognize significant changes in oxidative stress in diabetics, so it is necessary to consider alternatives that can be combined with modern drugs that have potential as antioxidants. The use of antioxidants (flavonoids and oleanolic acid) in DM therapy is an approach that needs to be considered as an effort to reduce oxidative stress and prevent complications such as atherosclerosis (Moustafa, 2003).

This study still has limitations, including not knowing for sure the long-term effects of giving the *Jamblang* fruit extract as an anti-hyperlipidemia treatment.

Conclusion

Jamblang fruit extract at doses of 125 mg/kgBW, 250 mg/kgBW, and 500 mg/kgBW, respectively, had an effect on reducing the AI of white rats (*Rattus norvegicus L.*) with male Wistar strain-induced alloxan. The *Jamblang* fruit extract at a dose of 500 mg/kg BW was able to reduce the most effective atherogenic index to 0,42.

Advice, the *Jamblang* fruit extract can be used as an alternative to therapy to reduce the risk of atherosclerosis, especially in patients with diabetes mellitus. Further study related to the quantitative phytochemical testing of metabolic compounds contained in the *Jamblang* extract and clinical trials to reduce the risk of atherosclerosis in patients with diabetes mellitus can be carried out.

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